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EFFECT OF ANTI-OSTEOPOROTIC DRUGS IN PREVENTION OF BONE FRACTURE: A SCOPING REVIEW

Mohammad Ali mohammad Almutlg[1]*, Shuwail Mahdi Shuwail Al Mahamdh[1], Hadi mohammad Hadi Almutif[1], Mubark HASAN Mubark Alsagoor[1], Mohammad mani hussen Alsagoor[1], Ibrahim Muhammad Alsaqour[1]

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Abstract

Introduction: Fragility fractures due to osteoporosis account for 9 million of the total fractures registered annually worldwide. Osteoporosis can be successfully treated with both antiresorptive and anabolic drugs, whose efficacy in reducing fracture incidence. Despite this, only a small proportion of osteoporotic patients are currently treated for fracture prevention. This scoping review describes how osteoporosis and various categories of anti-osteoporotic drugs impact fracture healing.

Methods: We performed a systematic search of the available literature in MEDLINE In-Process and Other Non-Indexed Citations Embase.com, and Cochrane Central Register of Controlled Trials. For each separate anti-osteoporotic agent PubMed was searched for evidence from randomized clinical trials (RCTs) in patients and animal studies with osteoporosis on antiosteoporotic (antiresorptive). The main search was completed independently by four investigators. Criteria for inclusion/exclusion of studies were established prior to the literature search. Eligible for the systematic review were retrospective, observational prospective, and randomized controlled trials (RCTs), which investigated the efficacy of the antiosteoporotic drugs on fracture risk BMD.

Results: Earlier studies that demonstrated the anti-osteoporotic effect of drugs had limited sample size and focused on single fracture type and/or a specific anti-osteoporotic treatment regimen . There are also no comprehensive reviews that present the effectiveness of the existing anti-osteoporotic drugs in use for patients with osteoporotic fractures. We found animal studies, preclinical and clinical trials, in addition to three reviews.

Conclusions: A consistent proportion of osteoporosis patients did not receive specific treatment after a fracture, showing poor adherence to national guidelines on osteoporosis treatment. Osteoporosis drug treatment, and to a greater extent in combination with calcium/vitamin D, and adherence were correlated with lower risk of both re-fracture and all-cause mortality.

Keywords: Vitamin D, Medications, Osteoporosis, Bone fracture, Prevention

[1]*Nursing, Ministry of health

***Corresponding Author:** Mohammad Ali mohammad Almutlg
*Nursing, Ministry of health

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Introduction

Osteoporosis is a chronic disease characterized by a loss of bone strength and a subsequent increase of fracture risk . Osteoporosis is a chronic degenerative disease characterized by a decrease in bone mineral density and an alteration in the skeletal microarchitecture, which leads to an increased risk of developing fragility fractures . It is estimated that 200 million women worldwide suffer from osteoporosis and this condition is mainly observed in postmenopausal women [1]. Fragility fractures due to osteoporosis account for 9 million of the total fractures registered annually worldwide and have important consequences in terms of mortality and disability, with high health and social costs . The limitation in ambulation resulting from osteoporotic fractures accompanies chronic pain, loss of independence, and decreased quality of life [2].

Osteoporosis can be successfully treated with both antiresorptive and anabolic drugs, whose efficacy in reducing fracture incidence has been well documented in several large, randomized control trials (RCTs) [3]. Anti-fracture efficacy of anti-osteoporotic drugs is mainly related to a progressive increase in bone mineral density (BMD) and/or a bone microarchitecture improvement . Since many patients are first diagnosed with osteoporosis when presenting with a fragility fracture, it is important for clinicians to understand the potential impact that anti-osteoporotic medications may have on fracture healing [4].

The relationship between fracture healing and osteoporosis is complicated by numerous associated conditions including age, endocrine disorders, malignancies, hypogonadism, medications, and other factors, all of which may impact fracture healing [5]. Despite this, only a small proportion of osteoporotic patients are currently treated for fracture prevention [6].

The initial diagnosis of osteoporosis commonly occurs when a patient presents with a fragility fracture. To appropriately manage both the fracture and osteoporosis, it is essential to understand how osteoporosis medications influence fracture healing. This is particularly true in osteoporosis, which has been identified as a risk factor for impaired fracture healing [7]. Thus, osteoporotic medications are split into two major categories: the antiresorptive medications, consisting of bisphosphonates, denosumab, calcitonin, oestrogen, and selective oestrogen receptor modulators (SERMs), and the anabolic agents, which include parathyroid hormone (PTH) analogy and strontium ranelate (SR) [8]. Since remodelling is crucial to fracture healing, both classes of drugs have the potential to hinder or accelerate this process.

Antiresorptive drugs such as bisphosphonates (Bps) and denosumab (Dmab) reduce fracture risk by lowering the rate of bone remodelling until fewer BMUs are available to remove bone. Conversely, anabolic agents such as teriparatide (PTH 1-34) are able to reduce fracture risk by stimulating new bone formation in an attempt to directly restore bone volume and microstructure. Antiresorptive drugs such as bisphosphonates (Bps) and denosumab (Dmab) reduce fracture risk by lowering the rate of bone remodelling until fewer BMUs are available to remove bone. Conversely, anabolic agents such as teriparatide (PTH 1-34) are able to reduce fracture risk by stimulating new bone formation in an attempt to directly restore bone volume and microstructure [9].

Despite recent interest in newer antiosteoporosis medications such as antisclerostin antibodies and cathepsin K inhibitors, reporting on their role in fracture healing would be premature due to limited and incomplete preclinical data [10]. Most animal studies examining the role of vitamin D have shown a positive effect on fracture healing. Animal studies have shown that osteoporosis can cause a significant reduction in fracture callus size, bone mineral density (BMD), and mechanical strength . Several studies have examined fracture healing in bisphosphonate-treated animals. These studies show that for fractures healing by endochondral ossification, bisphosphonates preferentially deposit at the acute fracture site and are able to increase callus and trabecular bone volume, as well as bone mineral content (BMC) during the reparative phase of bone healing [11]. This is in contrast to fracture healing via intramembranous ossification, a process in which biomechanical strength is more reliant on remodeling of trabecular bone.

In general, bone mass density (BMD) is a useful tool in assessment of fracture risk. In clinical practice, an increase in BMD is a sign of an adequate response to therapy, and it has been demonstrated that by increasing BMD, a significant reduction in fracture risk can be achieved [12]. BMD does not appear to offer reliability in patients with chronic diseases such as T2DM, since it has been reported to be either reduced , normal , or increased , compared with individuals without diabetes, highlighting the issue of reduced bone quality, due to deterioration in

bone microarchitecture [13]. This scoping review describes how osteoporosis and various categories of antiosteoporotic drugs impact fracture healing.

Methods

We performed a systematic search of the available literature in Ovid MEDLINE Ovid MEDLINE InProcess & Other Non-Indexed Citations Embase.com, and Cochrane Central Register of Controlled Trials. For each separate anti-osteoporotic agent PubMed was searched for evidence from randomized clinical trials (RCTs) in patients and animal studies with osteoporosis on anti-osteoporotic (antiresorptive) drugs lasting ≥ 3 years, followed by ≥ 1 year of followup and reported at least one item of the following: changes in BMD BTM and/or the risk of fractures after discontinuation of therapy. Each agent was searched separately in PubMed using its generic name (alendronate, zoledronic acid, risedronate, ibandronate, etidronate, raloxifene, bazedoxifene, teriparatide, abaloparatide, denosumab, strontium ranelate and romosozumab) combined with the term 'discontinuation'.

Each reference was reviewed, and if necessary, the abstract or full text was reviewed as well to check whether the study met our inclusion criteria. Three recent reviews on this topic were also checked for relevant references. The procedure concluded a manual search of key journals and abstracts from the major annual meetings in the field of diabetes, endocrinology, and osteoporosis. The main search was completed independently by four investigators. Criteria for inclusion/exclusion of studies were established prior to the literature search. Eligible for the systematic review were retrospective, observational prospective, and randomized controlled trials (RCTs), which investigated the efficacy of the anti-osteoporotic drugs on fracture risk BMD, and/or

BTM in postmenopausal women or men with osteoporosis. Information from each study was extracted independently by two reviewers using a standardized data extraction form.

Results and discussion

Earlier studies that demonstrated the anti-osteoporotic effect of drugs had limited sample size and focused on single fracture type and/or a specific anti-osteoporotic treatment regimen . There are also no comprehensive reviews that present the effectiveness of the existing anti-osteoporotic drugs in use for patients with osteoporotic fractures.

In animal models, the plasma concentration of 1,25dihydroxyvitamin D 3 (1,25(OH) D 3), one of the active vitamin D metabolites, rapidly decreases following a fracture. The other active metabolite, 24R,25-dihydroxyvitamin D 3 (24R,24(OH) D 3), may also have a key role in fracture healing. Furthermore, 24R,24(OH) D 3 -specific receptors have been identified in the healing callus and endochondral chondrocytes of animal models, suggesting the metabolite's specific role in fracture healing [14]. Mechanistically, the active metabolites of vitamin D act to increase new bone volume, callus volume and density, and trabecular number at the fracture site through various means. 1,25(OH) D 3 promotes osteogenic differentiation during early osteoblastogenesis and directly stimulates mineralization of the extracellular matrix through activation of osteoblast vitamin D receptors [15].

Animal studies using supraphysiologic doses of PTH have demonstrated increased strength and callus quantity in the fracture site. Although effective in treating osteoporosis, there are concerns that those doses (20-40 mcg total/dose) may not have the same effect on fracture healing as the supraphysiologic doses used in animal models (5-200 mcg/kg/dose). Animal models have shown SR incorporates into newly formed callus tissue, but the effect on fracture healing is dependent on bone quality. At this time, there is little published data regarding fracture healing in SR-treated patients. Understanding how various osteoporosis medications influence fracture healing is critical in the management of osteoporotic patients [16-18]. In a fracture healing model using ovariectomized rats, both StrRn and Teriparatide increased callus volume as compared with placebotreated controls, but only StrRn increased the mechanical strength of the callus [18].

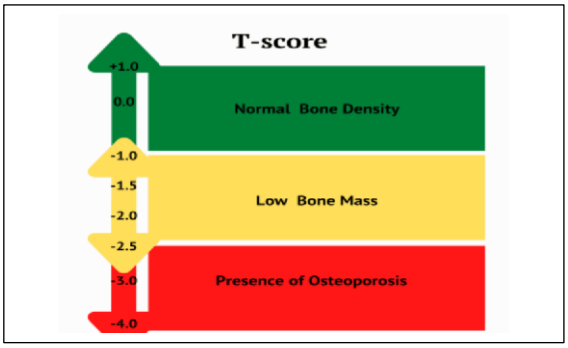
Clinical studies, although limited, also support the positive effect of calcium and vitamin D supplementation on fracture healing. Further support for the role of vitamin D in fracture healing comes from the study of non-union [16]. Although there is favorable evidence of calcium's effects on fracture healing, there is concern about its safety. Clinical studies evaluating the effect of bisphosphonates on fracture healing have shown that these agents yield no clinically significant difference in healing times through endochondral fracture repair. Two such studies showed that post-fracture bisphosphonate treatment led to increased BMD at the fracture site compared to placebo [19, 20]. This has prompted the treatment recommendation that bisphosphonates be started

between 2 and 12 weeks after a fragility fracture. To date, there has been little published clinical data regarding fracture healing in denosumabtreated patients. Calcitonin has been shown to be beneficial in treating osteoporosis by stabilizing or increasing BMD and reducing the risk of vertebral fracture by 33 % [21]. Although it is a controversial observation not well studied in relation to recovery from fracture, calcitonin has been seen to exert an analgesic effect, possibly by elevating endorphin levels or inhibiting neuropeptide release

During puberty they control the completion of bone growth, whereas decreasing oestrogen levels during menopause are associated with an imbalance between formation and resorption, causing loss of bone mass and an increased risk of fracture. Raloxifene and bazedoxifene currently have an approved indication for the treatment of postmenopausal osteoporosis due to their proven effects in bone remodeling reduction, bone mass increase or maintenance, and vertebral fracture risk reduction [22]. In phase 3 studies, romosozumab has shown marked increases in bone mass and reductions in the risk of fracture [23]. In the extension study of the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HOR-IZON) study, patients treated with zoledronic acid for 3 years were randomized to continue with zoledronic acid or placebo for another 3 years.

This bone turnover rebound raised the possibility of an imminent increase in fracture risk associated with impairment in bone microarchitecture [24]. Studies showed that patients combining anti-fracture drugs and calcium/vitamin D were more frequently on treatment with corticosteroids and analgesics, whereas they were less frequently exposed to vitamin K antagonists factor inhibitors [25].

Generally, abaloparatide has been shown to induce a marked BMD increase and reduce the incidence of vertebral and nonvertebral fractures . Therefore, in the ACTIVE study extension, the ability of antiresorptive agents to improve or maintain the benefit previously obtained with 18-month of abaloparatide treatment was evaluated [26]. Romosozumab is a humanized monoclonal antibody against sclerostin that increases bone formation and reduces bone resorption, improving BMD and bone strength in patients with postmenopausal osteoporosis. A phase 2 randomized clinical study showed that the 2-year administration of romosozumab to women with low BMD caused a



BMD gain that persisted for another year with denosumab (60 mg sc/6 months). Another sequential therapy based on the administration of romosozumab followed by an antiresorptive agent has been assessed. The best strategy has yet to be established. However, bisphosphonates are the only anti-osteoporotic drugs for which "drug holidays" may be considered, due to their bone tissue accumulation and their residual antifracture effect.

Two selected studies on zoledronic acid reported on fracture incidence and one showed that morphometric vertebral fracture risk was significantly lower in patients who received 6 years of treatment versus those who were treated with 3 years of zoledronic acid followed by 3 years of placebo. In the other study on risedronate, no vertebral fractures occurred and one traumatic fracture of the right proximal humerus due to a fall was reported as an adverse event in one patient in the 5-mg risedronate group . Two studies reported on fractures, but in the study of Black et al, only 6 women had a clinical fracture during year 2. This represents a reduction in relative risk of 37% in the 20µg teriparatide group and 42% in the 40-µg teriparatide group and it was concluded that vertebral fracture risk reduction by teriparatide administration persists for at least 18 months after discontinuation of therapy [27, 28]. Even using a greatly elevated annual hip fracture rate of 2% in

the model left almost 90% of the fracture risk reduction in women and more than 95% of the risk reduction in men unaccounted for [29].Treatment with PTH needed the fewest number of patients to prevent a secondary vertebral fracture, whereas the treatment with calcitonin needed the greatest number of patients [16].

A study found that patients receiving osteoporosisrelated drugs after a fracture had 44.4% lower risk of developing a subsequent fracture compared to untreated patients. Moreover, among treated patients, calcium/vitamin D supplement in addition to osteoporosis drug after a fracture was associated with a 64.4% lower risk of developing a subsequent fracture compared to the group receiving osteoporosis drug only [2]. A study conducted Kaplan-Meier analysis showed an increased probability of re-fracture In a study that compared the untreated group to the treated group and an increased probability of re-fracture in the osteoporosis drug only group compared to patients also combining calcium/vitamin D [2]. An increase in the transformation of woven bone into lamellar bone also takes place, resulting in improved callus remodeling compared to controls. This improved remodeling may be attributable to a theorized role for vitamin D as a regulator of osteoclastogenesis, based on the expression of vitamin D receptors by osteoclasts and the fact that 1, 25(OH) D3 stimulates osteoclast formation from bone marrow cell. At 6 weeks BMD was significantly higher in the treated group, indicating a positive impact of vitamin D and calcium supplementation on fracture healing . Nevertheless, it is important to keep in mind that calcium supplementation may not be inconsequential in fracture healing or osteoporosis management, particularly in elderly women with cardiovascular comorbidities. Serum levels of intact PTH may be monitored with a target of 20-40 pg/mL to ensure sufficient calcium and vitamin D intake, and prevent potential over-supplementation that may lead to increased cardiac risk [2]. The antifracture efficacy of bisphosphonates has been well documented: according to the Fracture Risk Intervention Trial, alendronate reduced the risk of vertebral fracture and hip fracture by over 70 and 50 %, respectively [30].

In fact, there are a limited randomized studies that have analyzed the impact on fracture rates of antiresorptive agents after teriparatide. Open-label follow-up studies after the Fracture Prevention Trial (FPT) have shown that the risk reduction persists for vertebral and nonvertebral fractures in women with osteoporosis initially randomized to teriparatide [31]. In spite of the aforementioned studies, the recent vertebral fracture treatment comparisons in Osteoporotic women (VERO) study has shown that vertebral and clinical fracture risk reduction associated with teriparatide treatment was not affected by previous bisphosphonate use [32].

Conclusions

A consistent proportion of osteoporosis patients did not receive specific treatment after a fracture, showing poor adherence to national guidelines on osteoporosis treatment. Osteoporosis drug treatment, and to a greater extent in combination with calcium/vitamin D, and adherence were correlated with lower risk of both re-fracture and all-cause mortality. Poor adherence to osteoporosis therapy could be partly explained by its long-term nature and the delayed perception of its benefit by the patient. Nevertheless, the risk of subsequent fracture is higher in nonadherent osteoporotic patients and this is of considerable interest considering that patients with previous fragility fracture are at a higher risk of developing a subsequent fracture.

Conflict of interests

The authors declared no conflict of interests.

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